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Interleukin-6 affects the severity of olfactory disorder: a cross-sectional survey of 148 patients who recovered from Omicron infection using the Sniffin' Sticks test in Tianjin, China

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ABSTRACT

Objectives: The mechanism of olfactory disorder (OD) in patients with COVID-19 is unclear. Our study aimed to elucidate the relationships between inflammatory factors and OD in a sample of patients infected with the Omicron variant, with a high vaccination rate in China.
Methods: The Sniffin' Sticks 12-item test was performed in a cross-sectional study of 148 recovered patients who were infected with the Omicron variant to evaluate OD severity. We compared demographic, laboratory, and clinical data.
Results: A total of 148 patients infected with the Omicron variant were enrolled. A total of 129 cases of OD were detected. Increased inflammation contributed to OD severity, especially in the adult group. OD was shown to be aggravated by an increase in interleukin-6 levels. The adjusted odds ratio (OR) was 2.22 (95% confidence interval 0.98-5.05, $P = 0.056$) after adjustment for age, sex, and vaccine characteristics.
Conclusion: These findings indicated that the prevalence of OD remains high in vaccinated patients infected with the Omicron variant and that the Sniffin' Sticks 12-item test might be a feasible method to screen for OD. Interleukin-6 may play a role in the biochemical and pathological processes underlying OD.

Introduction

The worldwide COVID-19 pandemic has continued for approximately 3 years, imposing severe burdens on global healthcare systems and economic stability. The main symptoms of COVID-19 are fever and cough (Guan *et al.*, 2020). In addition, an increasing number of studies have found that olfactory disorder (OD), which includes anosmia and hyposmia, is one of the most common clinical symptoms of COVID-19 and may be the first or only symptom in a patient (Eliezer *et al.*, 2020; Heidari *et al.*, 2020). OD occurs in 33-80% of patients with COVID-19 (Mao *et al.*, 2020; Wang *et al.*, 2020), which is higher than the prevalence of OD due to other upper respiratory tract infections (11-40%) (Welge-Lüssen and Wolfensberger, 2006). The inflammatory response and

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nasal epithelial damage may be the etiologies of nasal infection and inflammatory diseases, neurodegenerative diseases, and age-related OD (Chidambaram and Goh, 2017; Henkin *et al.*, 2013). Alterations in local immunity in the olfactory region have also been reported in patients with COVID-19-related OD (Torabi *et al.*, 2020). However, the exact pathophysiological mechanism of OD caused by COVID-19 is not yet clear.

Interleukin-6 (IL-6) is an important proinflammatory cytokine, and changes in the IL-6 level in body fluids occur during the development and occurrence of some diseases (Henkin *et al.*, 2013; Kiecolt-Glaser *et al.*, 2003). IL-6 is proposed to be one of the factors contributing to the cytokine storm in patients with severe COVID-19, and it may aggravate the disease and increase the incidence of complications (Han *et al.*, 2020). Therefore, the serum IL-6 level is widely considered an adverse prognostic factor for COVID-19. Currently, although researchers have suggested that IL-6 levels might play a role in the development of chronic OD, the relationship between IL-6 levels and OD in patients with COVID-19 has not been consistently documented (Cazzolla *et al.*, 2020; Sanli *et al.*, 2021; Vaira *et al.*, 2022).

Currently, vaccines are the most effective tool for protecting people against SARS-CoV-2 infection. As the safety and effectiveness in shortening the duration of symptoms after infection and promotion of virus clearance of vaccines have been widely reported, mass vaccination has been initiated worldwide (Andrews *et al.*, 2022; Lopez Bernal *et al.*, 2021; Thompson *et al.*, 2021;). Despite mass vaccination, literature reporting whether vaccines exert a protective effect on olfactory function is scarce.

This study conducted in Tianjin is based on a sample of patients with COVID-19 who were infected with the Omicron variant in Tianjin, China in 2022. This cross-sectional survey aimed to determine the relationship between IL-6 levels and OD after adjustment for demographic and vaccination-related confounders and to explore the role of vaccines in olfactory protection.

Methods

Patient enrollment

This study was approved by the research ethics committees of the Tianjin First Central Hospital (TFCH; approval number 2022N072KY). A total of 148 recovered patients who were previously infected with the Omicron variant were recruited from the TFCH between January 2022 and February 2022. All patients were transferred from the infectious disease hospital to TFCH for rehabilitation treatment when the polymerase chain reaction result turned negative. Before serum tests for IL-6 levels were conducted, these patients received approximately 14 days of symptomatic treatment, including oxygen therapy and traditional Chinese medicine therapy. Drugs, such as vitamin C, vitamin D, and glucocorticoids, that can change the levels of serum IL-6 were not used by any of the included patients (Feyaerts and Luyten, 2020; Silberstein, 2020; Xiang *et al.*, 2020). The severity of COVID-19 was determined according to the diagnostic and treatment guidelines for SARS-CoV-2 that were issued by the Chinese National Health Committee. The exclusion criteria used in this study included congenital anosmia, side effects of drugs (in particular, chemotherapy, and COVID-19 vaccination), previous surgery or radiotherapy damage, head injury, previous nasal diseases, systemic diseases (iron deficiency and autoimmune diseases), neurodegenerative disorders, or major depression.

The demographic and clinical variables recorded were age, sex, BMI, smoking history, vaccine type and dose, and whether they received a booster shot. The vaccine types include inactivated vaccines and adenovirus vaccines. The whole course of vaccination was defined as receiving two doses of inactivated vaccine or one dose of adenovirus vaccine, whereas receipt of one dose of inactivated vaccine or no vaccine was defined as incomplete-course vaccination. Receiving three doses of inactivated vaccine or two doses of adenovirus vaccine was defined as receiving a booster shot. Serum samples were collected from all patients after rehabilitation treatment (approximately 14 days after admission) for various tests, including routine blood tests and measurements of C-reactive protein (CRP) and IL-6 levels.

Olfactory testing

All patients retrospectively described olfactory function during COVID-19. The sinonasal outcome test 22 was used as a reference for the olfactory function assessment. The sinonasal outcome test 22 classified the severity of symptoms as none (0), very mild (1), mild or light (2), moderate (3), severe (4), or bad (5).

When the patients were about to be discharged from TFCH and polymerase chain reaction results were negative, olfactory function was assessed at suprathreshold levels with the Sniffin' Sticks 12-item test (SST-12) (Burghart Instruments, Wedel, Germany). This odor identification test uses 12 odor-dispensing felt-tip pens (Hummel *et al.*, 1997). An odor-dispensing pen was held in front of both nostrils for 3 to 4 seconds during the examination. After smelling the pen, the participants identified the presented odor by choosing from four visually presented answer alternatives (four forced choices). Refusal to answer or "do not know" were coded as incorrect. The number of correctly identified odors was coded as the odor identification score (0-12). We defined an SST-12 score $\geq$11 as normal, 10 $\geq$SST-12 $>$6 as hyposmia, or SST-12 $\leq$ 6 as anosmia based on the results of a large cohort study (Hummel *et al.*, 2001). Although olfactory abilities decrease at extreme ages, SST-12 may be used in those under the age of 10 years and above the age of 80 years. All tests were conducted with appropriate protective measures taken by examiners.

Statistical analysis

The data included in the study were analyzed with SPSS 22.0 software. The chi-square test was used to compare differences in demographics, odor identification results, the type and frequency of vaccination, and whether the patients received booster shots among the different OD groups. The Kruskal–Wallis test was used to compare differences in inflammation levels among the different OD groups. We then used the Cochran–Armitage trend test to analyze the association among different subgroups and the odor recognition rate. Multivariate ordinal polytomous logistic regression analysis was conducted to calculate the adjusted OR for OD in relation to blood inflammation indicators for the different OD groups. In model 1, the different OD groups were defined as the dependent variable, and blood indicators were defined as an independent variable. In model 2, age and sex adjustments were added to the parameters in model 1. In model 3, vaccination was adjusted and added to the parameters in model 2.

Results

Demographics and odor identification results

A total of 148 patients were included in the analysis (71 females and 77 males, mean age 31.99 $\pm$ 20.014 years). Anti-SARS-CoV-2 vaccination was performed with Sinovac vaccines (134 cases) and Ad5-nCoV vaccines (11 cases). Three patients did not receive any vaccine.

The SST-12 results revealed that patients with COVID-19 exhibited marked OD compared with published normative data. In contrast, only 8.1% of the patients were subjectively aware of OD. As

Table 1
Patient demographics among different olfactory disorder groups.

		N	Normal	Hyposmia	Anosmia	*P*
Sex	Male	71(48.0%)	8(47.1%)	53(48.2%)	10(47.6%)	0.996
	Female	77(52.0%)	11(52.9%)	57(51.8%)	9(52.4%)	
Smoking	No	135(91.2%)	15(47.1%)	103(93.6%)	17(81.0%)	0.203
	Yes	13(8.8%)	2(47.1%)	7(6.4%)	4(19.0%)	
	0-10	33(22.3%)	6(35.3%)	24(21.8%)	3(14.3%)	0.140
	11-20	19(12.8%)	2(11.8%)	15(13.6%)	2(9.5%)	
	21-30	20(13.5%)	1(5.9%)	17(15.5%)	2(9.5%)	
Age	31-40	31(20.9%)	3(17.6%)	26(23.6%)	2(9.5%)	
	41-50	13(8.8%)	3(17.6%)	7(6.4%)	3(14.3%)	
	51-60	17(11.5%)	2(11.8%)	10(9.1%)	5(23.8%)	
	61-70	10(6.8%)	0(0.0%)	9(8.2%)	1(4.8%)	
	70-80	4(2.7%)	0(0.0%)	1(0.9%)	3(14.3%)	
	81-90	1(0.7%)	0(0.0%)	1(0.9%)	0(0.0%)	
COVID-19	Mild	71(48.0%)	7(41.2%)	56(50.9%)	8(38.1%)	0.338
Disease	Ordinary	72(48.6%)	9(52.9%)	51(46.4%)	12(57.1%)	
Severity	Asymptomatic infection	4(2.7%)	1(25.0%)	3(2.7%)	0(0.0%)	
	Severe	1(0.7%)	0(0.0%)	0(0.0%)	1(4.8%)	
Smell	Yes	12(8.1%)	2(1.4%)	10(100.0%)	0(0.0%)	0.138
Complaints	No	136(91.9%)	136(98.6%)	0(0.0%)	0(0.0%)	

illustrated in Table 1, 129 (87.2%) of the 148 patients with COVID-19 were identified as having OD, including 110 with hyposmia (74.3%) and 19 with anosmia (12.8%). Most patients in our cohort showed hyposmia symptoms, potentially because the SST-12 was completed approximately 28 days after infection, and some patients with anosmia exhibited a slight recovery. In addition, the vast majority of patients in our cohort had a mild disease or were asymptomatic.

As shown in Table 1, smoking, sex, and disease severity were not significantly different among the different OD groups. Notably, we did not observe significant differences in age among the OD groups.

The odor recognition rate on the SST-12 was different among the different groups. In addition to orange and leather, other odors were correctly identified by more than 80% of the normal group (Supplementary Table 1). Except for oranges, all items had significantly different recognition rates among the three groups. The results suggest that the ability of patients with COVID-19 to recognize most odors is impaired to varying degrees.

Olfactory function is associated with inflammation levels in patients with COVID-19

We next analyzed inflammation levels in patients with COVID-19 subgrouped based on OD severity to examine whether higher inflammation levels contributed to OD severity. Comparisons among the different OD groups showed that IL-6 and CRP levels were significantly different between the anosmia and hyposmia groups ($P < 0.05$, Figure 1). Notably, the inflammation level increased with OD severity (Figure 1).

Multivariate ordinal polytomous logistic regression analysis of the association of IL-6 levels with OD

Elevated IL-6 levels significantly increased the risk of OD (OR = 2.312, 95% confidence interval: 1.343-3.979; Table 2). This relationship was robust after adjustment for age, sex, the type and dose of vaccine, and the number of booster shots (adjusted OR = 2.226). However, other inflammatory indicators, such as CRP, immunoglobulin G, and immunoglobulin M levels, did not significantly increase the risk of OD ($P > 0.05$) (Table 3).

Relationship between olfactory function and inflammation levels in different age subgroups

We included many children in our study, and differences in olfactory and immune responses may exist between children and adults. We compared the difference in the relationship between inflammatory levels and OD between children and adults. In the adults, the IL-6 level, neutrophil-to-lymphocyte ratio (NLR), and CRP level were significantly different among the different groups ($P < 0.05$; Figure 2). This difference may be due to the limited sample size and the fact that the included patients were in the convalescence stage. Notably, the inflammation level increased with OD severity (Figure 2). In children, no significant differences in the levels of major inflammatory indicators were observed between the groups. However, children with OD showed lower inflammation levels than children with normal olfactory function (Supplementary Figure 1). This finding differed from the results obtained for adults, and larger sample sizes are needed to assess the validity of this finding.

Discussion

Using the validated SST-12, we quantified olfactory function in a sample of recovered patients who were previously infected with the Omicron variant in Tianjin, China, in 2022. OD is still the most common symptom of vaccinated patients, suggesting that the mechanism of OD may be independent of the protective effect of the vaccine. Quantitative olfactory testing might be an effective method for the early identification of patients infected with Omicron. Our survey showed that elevated inflammation levels contributed to OD severity in the adult subgroup. Notably, this relationship seemed inconsistent between the children and adult subgroups. This relationship was not statistically significant in the child subgroup. Compared with the normal group, the OD groups had higher IL-6 levels. This relationship was robust after adjustment for demographic and vaccination confounders.

In our study, 87.2% of the patients were identified as having OD, whereas only 8.1% of patients were subjectively aware of OD. The exact prevalence is much higher than the self-reported prevalence. This result suggests significant differences between subjective and objective methods of olfactory function assessment. This finding is consistent with the conclusion reported by Moein *et al.* (2020) Previous studies suggest that the prevalence of OD in patients with

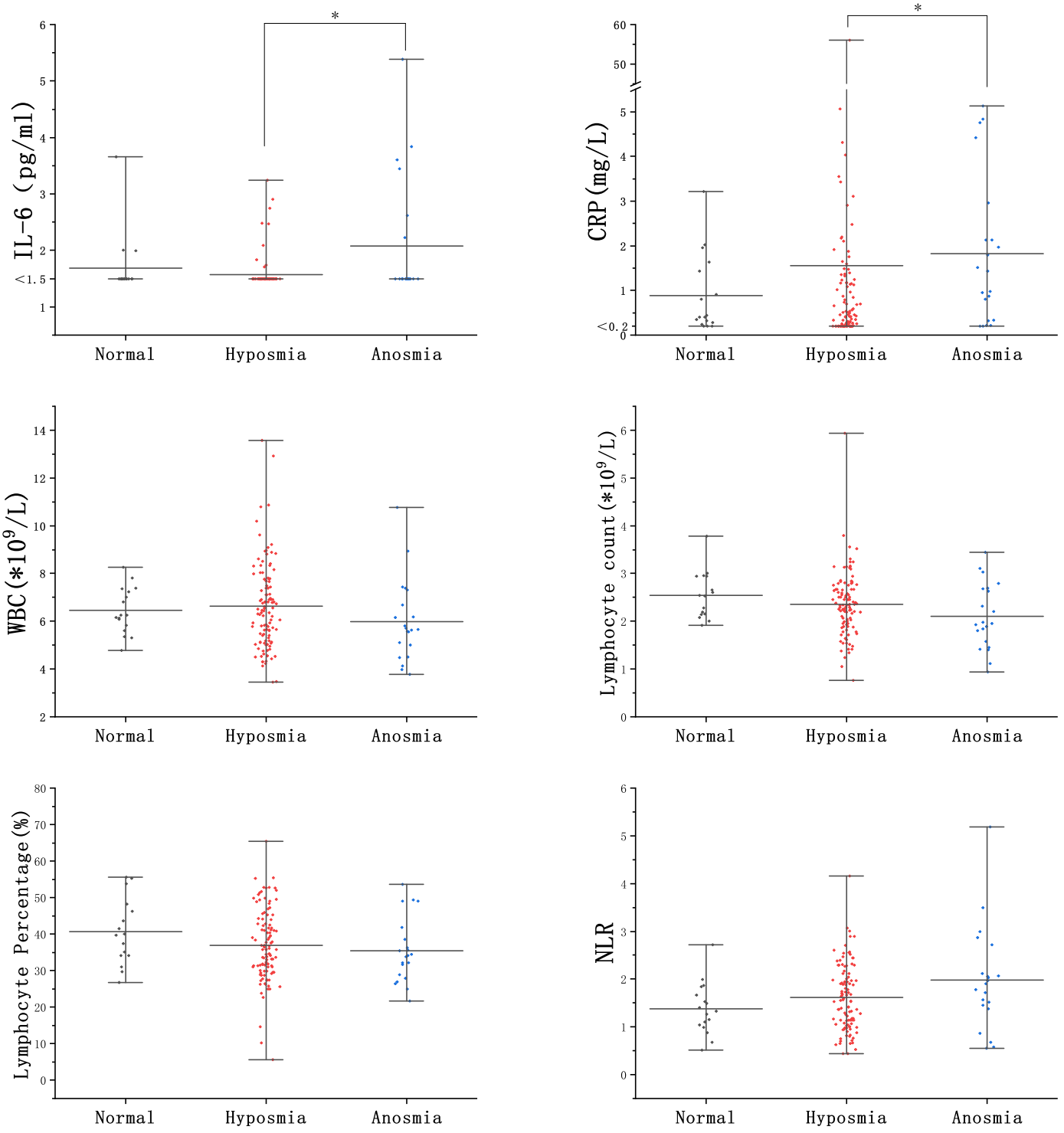

Figure 1. The inflammatory levels in patients with COVID-19 with different OD severity. A total of 148 COVID-19 patients were divided into three groups: anosmia, hyposmia, and normal. The serum levels of WBC, lymphocyte counts, lymphocyte percentages, CRP, IL-6, and NLR were analyzed approximately 14 days after admission. Median with range was presented.
NLR, neutrophil-to-lymphocyte ratio; OD, olfactory disorder; WBC, white blood cells.

COVID-19 varies widely, ranging from 33-80% (Mao *et al.*, 2020; Meng *et al.*, 2020; Wang *et al.*, 2020). We analyzed the reasons and found that quantitative olfactory tests have always been the main method for diagnosing OD; however, most previous surveys were conducted using noncontact methods, such as online questionnaire surveys and telephone interviews, which may lead to deviations in the results. Thus, OD remains an important feature of COVID-19 after vaccination, and a quantitative olfaction test may be a quick and inexpensive alternative diagnostic tool to screen for COVID-19 in a large number of individuals.

Our survey showed that higher inflammation levels contributed to OD severity. After adjustment for confounding factors, such as age, sex, type and dose of vaccine, and booster shots, we found that elevated IL-6 levels significantly increased the risk of OD,

Table 2
Multivariate ordinal polytomous logistic regression analysis of IL-6 for OD.

	Factor	E	SE	Wald	*P*-value	OR	95% CI
Model 1	**IL-6**	0.838	0.277	9.144	0.002	2.312	1.343-3.979
	CRP	0.015	0.060	0.061	0.805	1.015	0.902-1.141
	IgG	0.006	0.008	0.513	0.474	1.006	0.990-1.021
	IgM	0.016	0.031	0.265	0.607	1.016	0.956-1.081
	WBC	-0.196	0.231	0.717	0.397	0.822	0.523-1.293
Model 2	**IL-6**	0.704	0.344	4.190	0.041	2.022	1.030-3.967
	CRP	-0.071	0.094	0.581	0.446	0.931	0.775-1.119
	IgG	-0.005	0.006	0.733	0.392	0.995	0.984-1.006
	IgM	0.010	0.036	0.074	0.786	1.010	0.941-1.084
	WBC	-0.346	0.223	2.396	0.122	0.708	0.457-1.096
Model 3	**IL-6**	0.800	0.419	3.644	0.056	2.226	0.979-5.053
	CRP	-0.087	0.117	0.556	0.456	0.917	0.728-1.153
	IgG	-0.020	0.008	5.950	0.015	0.980	0.964-0.996
	IgM	0.005	0.020	0.058	0.810	1.005	0.966-1.046
	WBC	-0.016	0.205	0.006	0.938	0.984	0.658-1.473

Model 1, different OD groups were defined as the dependent variable, and blood indicators were defined as an independent variable. Model 2: age and sex adjustments were added to model 1. Model 3: vaccination was adjusted and added to model 2.
CI, confidence interval; OD, olfactory disorder; OR, odds ratio; WBC, white blood cells.

Table 3
Comparisons of vaccination statuses among different olfactory disorder groups.

		N	Normal	Hyposmia	Anosmia	*P*
< 18 years	**One/two does**	50	7(14.0%)	38(76.0%)	5(10.0%)	0.762
	Booster shots	1	0(0%)	1(100%)	0(0%)	
	Whole-course vaccination	47	6(12.8%)	37(78.7%)	4(8.5%)	0.468
	Incomplete-course vaccination	4	1(25.0%)	2(50.0%)	1(25.0%)	
≥ 18 years	**one/two does**	42	2(4.8%)	33(78.6%)	7(16.7%)	0.286
	Booster shots	55	8(14.5%)	38(69.1%)	9(16.4%)	
	Whole-course vaccination	85	10(10.9%)	66(71.7%)	16(17.4%)	0.200
	Incomplete-course vaccination	5	0(0%)	5(100%)	0(0%)	
	Inactivated vaccines	84	10(11.9%)	59(73.1%)	15(14.9%)	0.172
	Adenovirus vaccine	11	0(0%)	10(90.9%)	1(9.1%)	

and this relationship was robust. IL-6 is part of a complex signaling system that plays multiple roles in metabolism (Henkin *et al.*, 2013). It drives the production of acute phase proteins, including CRP and fibrinogen, induced by systemic inflammation (Koukkunen *et al.*, 2001). IL-6 has been shown to be a negative prognostic indicator in patients with COVID-19 (Han *et al.*, 2020). In addition, Henkin *et al* found that IL-6 was significantly increased in the plasma, saliva, and nasal mucus of patients with OD (Henkin *et al.*, 2013). An analysis of these changes may be related to local or systemic inflammatory processes, which may be the cause or result of OD-related pathological processes. Currently, few studies have focused on the relationship between OD and IL-6 levels in patients with COVID-19 (Cazzolla *et al.*, 2020; Sanli *et al.*, 2021; Vaira *et al.*, 2022). Several studies have found that IL-6 plays an important role in the OD of patients with COVID-19. However, Vaira *et al* did not identify any correlation between OD and COVID-19 using psychophysical olfactory scores (Vaira *et al.*, 2022). In our analysis, this difference may be because olfaction is potentially affected by a variety of confounding factors, such as age and sex. The effects of these confounding factors were not fully considered in previous studies, thus resulting in differences in the final results. Our findings are consistent with OD results from studies of other types of chronic inflammation. We hypothesized that elevated IL-6 levels might be considered a possible causal factor for initiating OD after local or systemic infection due to immunological and inflammatory changes.

We did not observe significant differences between the OD groups at different ages. Previous studies suggested that olfactory function in older individuals is worse than that in young individuals. Our analysis suggests that this Omicron outbreak mainly occurred among children and their parents, and fewer older people were infected. Therefore, the study population may not accurately reflect the true characteristics of the whole population. Given that we had a large number of children in our sample, we compared the difference in the relationship between inflammation levels and OD among children and adults. In the subgroup analysis, the levels of IL-6 and CRP and the NLR in adults increased with the OD severity. However, children showed the opposite trend; although, the difference was insignificant. Based on this result, children may have different OD mechanisms than adults, and further research is needed in the future.

To the best of our knowledge, this study is the first to investigate the prevalence of OD in vaccinated patients with COVID-19. OD is still the most common symptom occurring in vaccinated individuals, suggesting that the mechanism of OD may be independent of the protective effect of the vaccine. Vaccination potentially reduces other symptoms and prevents life-threatening lung damage and complications, but OD is not avoidable, according to current research. Therefore, we must pay attention to OD in patients infected with the Omicron variant. Previous studies have reported that viruses were detected in the nasal epithelial cells of patients with OD after viral infection and that the level of IL-6 in the nasal lavage fluid of patients with OD increased (Henkin *et al.*, 2013; Tian *et al.*, 2021; Wang *et al.*, 2007). IL-6 may be an endogenous substance that regulates olfactory neuron activity because it has been shown to regulate the activity of neurons and glial cells (Galiano *et al.*, 2001; Jüttler *et al.*, 2002). Similarly, the nasal cavity is an important area susceptible to SARS-CoV-2 infection (Sungnak *et al.*, 2020). SARS-CoV-2 enters nasal epithelial cells and may subsequently initiate a rapid immune response in the host body, pre-

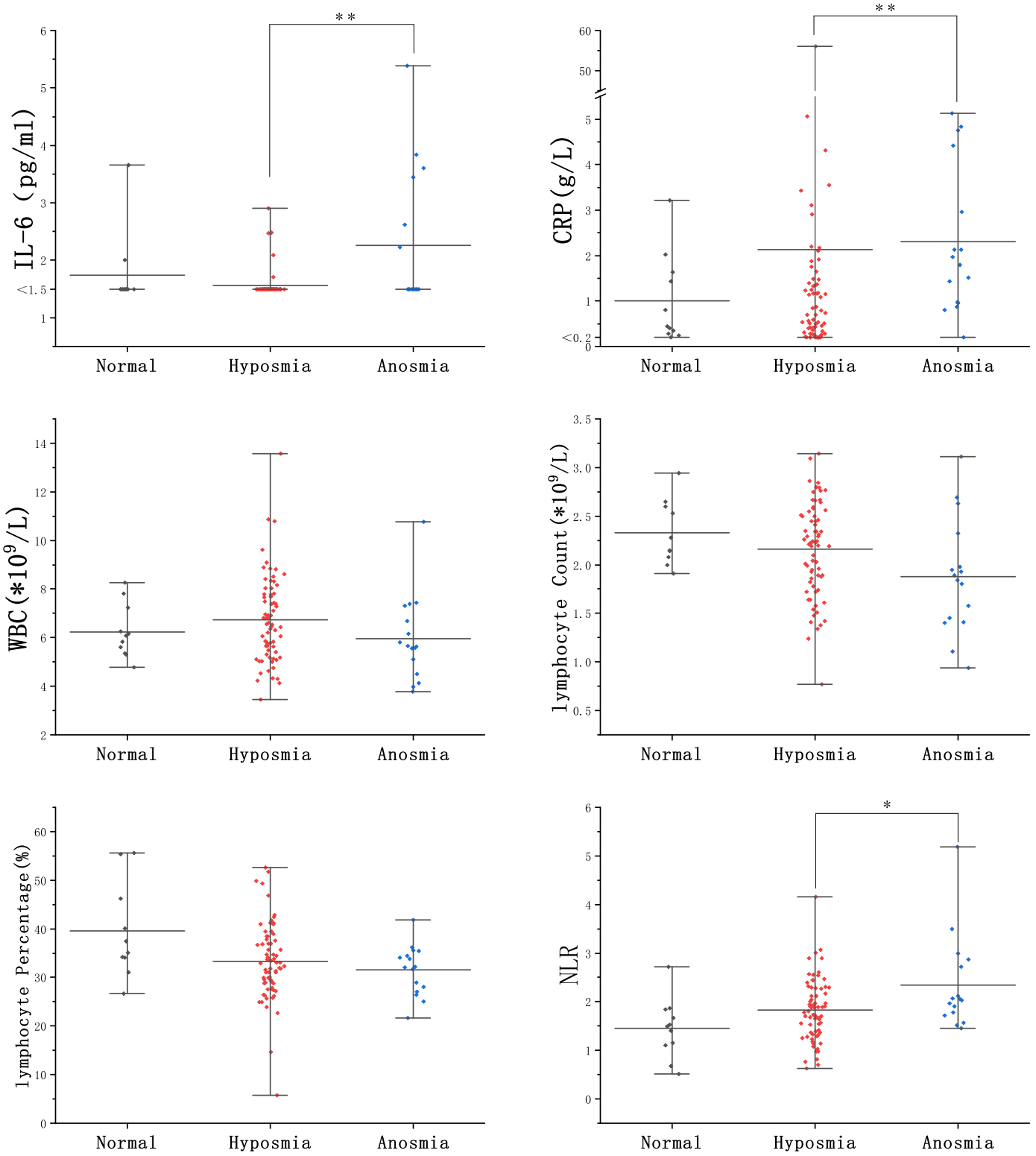

Figure 2. The inflammatory levels in the adult group with different OD severity. A total of 97 patients with COVID-19 were divided into three groups: anosmia, hyposmia, and normal. The serum levels of WBC, lymphocyte counts, lymphocyte percentages, CRP, IL-6, and NLR were analyzed. Median with range was presented.
NLR, neutrophil-to-lymphocyte ratio; OD, olfactory disorder; WBC, white blood cells.

senting as OD. The nasal cavity is also frequently the first route of initial infection. Therefore, changes in the local immune microenvironment after infection may be an important factor contributing to the weak olfactory protection of the vaccine. In the future, we must focus on OD treatment even if patients with COVID-19 have been vaccinated.

This study has some limitations. First, as clinical indicators of disease severity, IL-6 and CRP levels were considered to return to normal when the levels were less than 1.5 pg/ml and 0.2 g/l, respectively. IL-6 and CRP levels were obtained from hospital tests in our study. Therefore, IL-6 levels less than 1.5 pg/ml and CRP levels less than 0.2 g/l were not shown. Second, this study used

a cross-sectional design to explore the relationship between IL-6 levels and OD in individuals who recovered from COVID-19. Therefore, the temporal evolution of both IL-6 levels and OD was not the focus of this study. We will conduct a cohort study to determine the changes in IL-6 levels and OD over time in the future. Third, due to exposure problems, we did not detect the level of IL-6 in nasal lavage fluid and were unable to recognize changes in the local immune environment. Finally, the SST-12 test is a screening test for olfactory function, and its assessment of olfactory function was weaker than that of the Sniffin' Sticks test and the 40-item University of Pennsylvania Smell Identification Test (UPSIT). However, SST-12 has been applied to assess the olfactory function of patients with COVID-19 and has good consistency with UPSIT (Moein *et al.*, 2020). We will use Sniffin' Sticks test or UPSIT in future follow-up studies to further evaluate the olfactory function of patients. In addition, because of the hospital environment and epidemic prevention policy and considering the detection environment and patient cooperation, the butanol threshold test is a noninvasive, rapid, and objective method to determine the olfactory function and may be another option for olfactory assessment to reduce the risk of transmission or transmission of the disease. In a future follow-up study, we will conduct further tests using the two test methods described previously.

Conclusion

Although a high vaccination rate has been recorded in patients infected with the Omicron variant, the prevalence of OD remains high, and we must pay attention to OD in patients infected with the Omicron variant. The SST-12 is a reliable tool to assess olfactory function in patients with COVID-19. Elevated IL-6 levels might significantly increase the risk of OD and may be involved in the development of OD in patients infected with the Omicron variant. These changes may be related to local or systemic inflammatory processes, which are a potential cause or a result of pathological processes associated with OD. These results support the concept that OD has a biochemical basis and that IL-6 may play a role in the biochemical and pathological processes underlying OD and its treatment.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Author contributions

YL, XM, WW, and ZS all developed the study concept and design. MK, JZ, ZZ, MB, and PL recruited patients, collected specimens, and collected clinical metadata. YL, XM, WW, and ZS were major contributors in writing the manuscript and reviewing it critically. The authors read and approved the final manuscript.

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Ethical approval

This study was approved by the institutional review board of the Tianjin First Central Hospital, Tianjin, China. This study was performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.07.074.

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